BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

TRANSLATION

(19) PATENT BUREAU OF JAPAN (JP)

(12) OFFICIAL GAZETTE FOR EXAMINED PATENTS (B)

(11) Japanese Patent Application Publication Kokoku: S42-11,753 (1967)
(43) Publication Date: July 4, 1967
No. of Invention: 1 (Total of 3 pages)

(54) PROCESS FOR THE PRODUCTION OF NOVEL 7-METHYLAMINOPYRAZOLO[1,5-A]PYRIMIDINE DERIVATIVE

(21) Application Number: S39-2,594 (1964)
(22) Application Date: January 20, 1964

(72) Inventor: A.. Takamizawa
73-6 Shimohozumi
Ibaraki City

Y. Hamashima
26-2 Keikon-cho
Ukyo-ku, Kyoto City

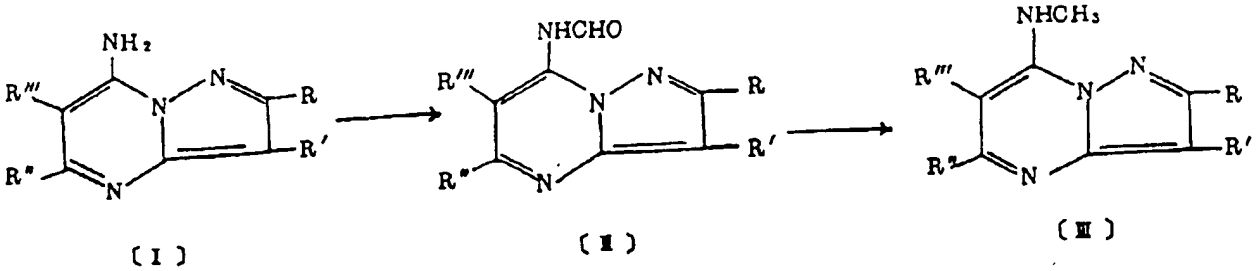
(71) Applicant: Shionogi Seiyaku K.K.
3-12 Dosho-machi
Higashi-ku, Osaka City
Representative: K. Takeda

(74) Patent Attorney: M. Iwasaki

Detailed explanation of the invention

This invention pertains to a process for the production of a novel 7-methylaminopyrazolo[1,5-a]-pyrimidine, and the objective of this invention is to manufacture a compound useful as a drug.

The point in the process of this invention is found in the reaction of 7-aminopyrazolo[1,5-a]-pyrimidine which may have alkyl, alkenyl, aryl or aralkyl groups at all or part of the positions 2, 3, 5 and 6 or not at all with a formylation agent to prepare a 7-formylamino compound which is subsequently reduced to a 7-methylamino compound, and this process is shown by the following general formulae.



(I) (II) (III)

(In the formulae, R, R', R" and R"' are respectively hydrogen atoms, alkyl groups, alkenyl groups, aryl groups or aralkyl groups.)

The starting substance [I] in the process of this invention is 7-aminopyrazolo[1,5-a]pyrimidine which may have alkyl, alkenyl, aryl or aralkyl groups at all or part of the positions 2, 3, 5 and 6 or not at all, and the substituent represented by R, R', R" and R"' may be identical or different to one another. Specific examples of these hydrocarbon groups include methyl group, ethyl group, propyl group, isopropyl group, butyl group, allyl group, butenyl group, phenyl group, toluyl group, benzyl group, phenetyl group, etc.

In the process of this invention, the first work unit is formylation, and as a formylation agent, formic acid-containing mixed acid anhydride is used. The use of formic acid-acetic acid mixed acid anhydride is preferable. This reaction is carried out in a suitable non-reactive solvent or no reaction solvent (in this case, the formylation agent may be used as a solvent) allowing the starting material [I] to react with a formylation agent at room temperature. The reaction time is suitably 1-2 days, and if it is longer, or the formylation agent is used in an excess amount, the formation of a di-formylated compound is observed.

The formylated compound [II] prepared here is subsequently reduced to obtain a desired methylamino compound [III]. This reduction reaction is carried out by using a metal hydride complex compound, especially lithium aluminum hydride, and practically, those procedures used for this type of reduction may be used. The reaction is preferably carried out under a moderately heated condition in a solvent such as ether, tetrahydrofuran, etc.

All of the products, 7-methylaminopyrazolo[1,5-a]pyrimidine derivatives are novel compounds, have analgesic action, anti-inflammatory action, etc., and thus, they are useful as a drug or synthetic intermediate.

The practical mode of the process of this invention is explained by using application examples as follows.

Application example 1

(a) To 1.0 g of 2,3-dimethyl-7-aminopyrazolo[1,5-a]pyrimidine, 5 ml of formic acid-acetic acid mixed acid anhydride (prepared by carrying out the reaction of formic acid and acetic anhydride) was added while cooling in an ice water bath. After the cooling bath was subsequently removed, and the reaction mixture was allowed to stand at room temperature for 1.5 days, it was concentrated under vacuum, and the crystalline residue obtained was recrystallized from acetone to obtain 0.95 g of pale green crystalline 2,3-dimethyl-7-formylaminopyrazolo[1,5-a]pyrimidine having m.p. 189°C (foaming).

Result of elemental analysis as $C_9H_{10}ON_4$

Calculated	C: 56.83, H: 5.30, N: 29.46
Observed	C: 56.95, H: 5.38, N: 29.11

(b) To 50 ml of tetrahydrofuran, 0.7 g of lithium aluminum hydride was added, and a solution of 1.0 g of 2,3-dimethyl-7-formylaminopyrazolo[1,5-a]pyrimidine dissolved in 30 ml of tetrahydrofuran was added in drops while cooling in an ice water bath. Subsequently, the reaction mixture was heated and stirred at 70°C for 5 hrs, and a sodium hydroxide solution was added to carry out decomposition of the reducing agent. The tetrahydrofuran layer was concentrated, extracted with chloroform, washed with a sodium hydroxide solution and dried with magnesium sulfate. After distilling off the solvent, the residue was recrystallized from ether to obtain 0.83 g of 2,3-dimethyl-7-methylaminopyrazolo[1,5-a]pyrimidine in a colorless plate crystalline form having m.p. 146°C.

Result of elemental analysis as $C_9H_{12}N_4$

Calculated	C: 61.34, H: 6.86, N: 31.80
Observed	C: 61.50, H: 7.01, N: 31.80

Application example 2

(a) The reaction of 2.0 g of 2,3,6-trimethyl-7-aminopyrazolo[1,5-a]pyrimidine and 10 ml of formic acid-acetic acid mixed acid anhydride was carried out similarly to the previous example. After standing at room temperature for one day, the reaction mixture was concentrated under vacuum, and the residue was recrystallized from acetone to obtain of 1.6 g of pale green crystalline 2,3,6-trimethyl-7-formylaminopyrazolo[1,5-a]pyrimidine having m.p. 183°C (foaming).

Result of elemental analysis as $C_{10}H_{12}ON_4$

Calculated	C: 58.81, H: 5.92, N: 27.44
Observed	C: 58.79, H: 6.10, N: 27.53

(b) In tetrahydrofuran, 250 mg of 2,3,6-trimethyl-7-formylaminopyrazolo[1,5-a]pyrimidine was reduced similarly to the previous example by using 200 mg of lithium aluminum hydride, and the crude product was recrystallized from acetone to obtain 205 mg of 2,3,6-trimethyl-7-methylaminopyrazolo[1,5-a]pyrimidine in a colorless plate crystalline form having m.p. 157°C.

Result of elemental analysis as $C_{10}H_{14}N_4$

Calculated	C: 63.13, H: 7.42, N: 29.25
Observed	C: 63.24, H: 7.42, N: 29.16

Application example 3

(a) To 1.2 g of 2,5-dimethyl-3-phenyl-7-aminopyrazolo[1,5-a]pyrimidine, 20 ml of formic acid-acetic acid mixed acid anhydride was added while cooling in an ice water bath. After the cooling bath was subsequently removed, the reaction mixture was stirred at room temperature for 8 hrs and allowed to stand at room temperature overnight, it was concentrated under vacuum. After washing with ether, the crystalline residue obtained was recrystallized from acetone to obtain 1.12 g of pale yellow cubic crystalline 2,5-dimethyl-3-phenyl-7-formylaminopyrazolo[1,5-a]pyrimidine having m.p. 189°C (foaming).

IRν_{max}(Nujol) cm^{-1}: 3176, 1700, 1613

(b) In tetrahydrofuran, 1.0 g of 2,5-dimethyl-3-phenyl-7-formylaminopyrazolo[1,5-a]pyrimidine was reduced similarly to the previous example by using 0.7 g of lithium aluminum hydride, and the crude product was recrystallized from acetone to obtain 0.82 g of 2,5-dimethyl-3-phenyl-7-methylaminopyrazolo[1,5-a]pyrimidine in a colorless prism crystalline form having m.p. 190-191°C.

IRν_{max}(Nujol) cm^{-1}: 3215, 1629, 1587, 770

Example 4

(a) To 0.75 g of 2-benzyl-3,,5-dimethyl-7-aminopyrazolo[1,5-a]pyrimidine, 15 ml of formic acid-acetic acid mixed acid anhydride was added while cooling in an ice water bath. After the cooling bath was subsequently removed, the reaction mixture was stirred at room temperature for 5 hrs and allowed to stand at room temperature overnight, it was concentrated under vacuum. After washing with ether, the crystalline residue obtained was recrystallized from acetone to obtain 0.64 g of colorless rhombic crystalline 2-benzyl-3,5-dimethyl-7-formylaminopyrazolo[1,5-a]pyrimidine having m.p. 131-132°C.

IRν_{max}(Nujol) cm^{-1}: 3200, 1691, 1624, 1178, 1167, 1129

(b) The reduction of 540 mg of 2-benzyl-3,5-dimethyl-7-formylaminopyrazolo[1,5-a]pyrimidine was carried out in tetrahydrofuran similarly to the previous example by using 400 mg of lithium aluminum hydride to obtain 2-benzyl-3,5-dimethyl-7-methylaminopyrazolo[1,5-a]pyrimidine as an oily compound.

IRν_{max}(Nujol) cm^{-1}: 3400, 1625,1593, 1095

Picrate: yellow columnar crystal with m.p. 207-208°C

Patent Claim

Process for the production of novel 7-methylaminopyrazolo[1,5-a]-pyrimidine characterized by carrying out the reaction of 7-aminopyrazolo[1,5-a]pyrimidine having substituents at the 2,3,5 and 6 positions or no substituent at all with a formylation agent to form a corresponding 7-formylamino compound, which is subsequently reduced with a metal hydride complex compound to obtain a 7-methylamino compound.

PTS SERVICES, INC.
705 CONCORD AVE., SUITE 170
WILMINGTON, DE 19802

PTS

10-15-97

P. Gilligan

1185-264-627 000664.200000

Ms. Linda Grim
Information Services
Du Pont Merck Pharmaceutical Co.
Du Pont Merck Plaza
Maple Run 1133

TRANSLATION REQUEST NO. **70156**

For translation per above TR No. of JP-42-11753 (Japanese Patent)

1440 words total at the arte of 12.5¢ per word ..... $ 180.00

Thank you for the oportunity to be of help.

Sincerely,

PTS Services, Inc.

TEL (302) 764-6103
FAX (302) 764-6216

公告　昭 42. 7. 4
（全3頁）

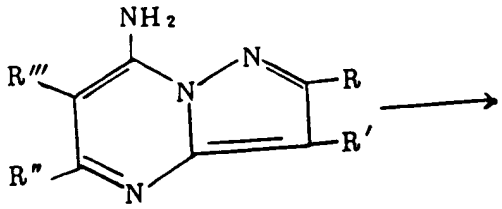
新規7－メチルアミノピラゾロ〔1，5－a〕ピリミジン誘導体の製造法

特　　願　昭　39－2594
出 願 日　昭　39．1．20
発 明 者　高見沢映
茨木市下穂積73の6
同　浜島好男
京都市右京区桂坤町26の2
出 願 人　塩野義製薬株式会社
大阪市東区道修町3の12
代 表 者　武田健一
代 理 人　弁理士　岩崎光隆

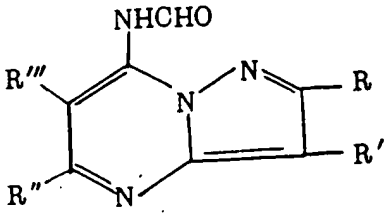
発明の詳細な説明

本発明は新規7－メチルアミノピラゾロ〔1,5－a〕ピリミジン誘導体の製造法に関し、医薬として有用な化合物を製造することを目的とする。

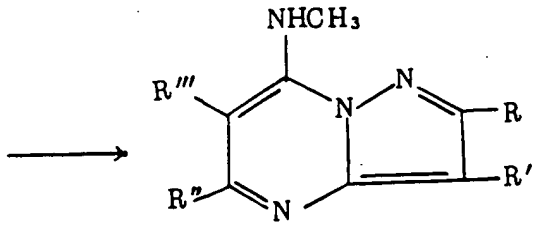
本発明方法の要旨は2位、3位、5位、6位の全部または一部にアルキル基、アルケニル基、アリール基またはアラルキル基を有しまたは有しない7－アミノピラゾロ〔1,5－a〕ピリミジンをホルミル化剤と反応させて7－ホルミルアミノ体とし、次いでこれを還元して7－メチルアミノ体に変ずる点にあり、その過程は次の一般式によつて示される。



〔Ⅰ〕



〔Ⅱ〕



〔Ⅲ〕

〔式中、R、R′、R″、およびR‴はそれぞれ水素、アルキル基、アルケニル基、アリール基またはアラルキル基を表わす。〕

本発明方法の原料物質〔Ⅰ〕は2位、3位、5位、6位の全部または一部にアルキル基、アルケニル基、アリール基またはアラルキル基を有しあるいはこれらの位置に置換基を全く有しない7－アミノピラゾロ〔1,5－a〕ピリミジンであつて、R、R′、R″およびR‴で表わされる置換基は互いに同一であつても異つていてもよい。これらの炭化水素基の具体例としては、メチル基、エチル基、プロピル基、イソプロピル基、ブチル基、アリル基、ブテニル基、フエニヌ基、トルイル基、ベンジル基、フエネチル基などを例示することができる。

本発明方法の第1工程はホイミル化反応であつて、ホルミル化剤としてはギ酸を含む混合酸無水物が使用される。ことにギ酸酢酸混合酸無水物が好適である。本反応は適当な非反応性溶媒中あるいは反応溶媒を使用することなく（この場合はホルミル化剤に溶媒を兼ねさせてもよい）原料物質〔Ⅰ〕とホルミル化剤を室温で反応させればよい。反応時間は1～2日程度が適当であつて、それ以上の時間をかけるとホルミル化剤を過剰に使用した場合ジホルミル化体の生成が見られる。

次いでここに得られたホルミル化体〔Ⅱ〕を還元すれば目的とするメチルアミノ体〔Ⅲ〕が得られる。この還元反応は水素化金属錯化合物、ことに水素化アルミニウムリチウムを使用して行うのがよく、実際上はこの種の還元反応において常用される操作手段に従つて実施されればよい。特にエーテル、テトラヒドロフランなどを溶媒として温和な加熱下に還元するのが適当である。

かくして得られる7－メチルアミノピラゾロ

物であつて、鎮静作用、抗炎症作用などを有するので医薬またはその合成中間体として有用である。

以下に実施例を挙げて本発明方法実施の態様を示す。

例　1

(イ) 氷水で冷却しながら2,3－ジメチル－7－アミノピラゾロ〔1,5－a〕ピリミジン1.0gにギ酸酢酸混合酸無水物（ギ酸と無水酢酸を反応させて製造する）5mlを加える。冷却浴を去り、室温に1.5日放置した後減圧濃縮し、結晶性残渣をアセトンより再結晶すれば、mp189℃（発泡）の淡緑色針状晶として2,3－ジメチル－7－ホルミルアミノピラゾロ〔1,5－a〕ピリミジン0.95gを得る。

元素分析　$C_9H_{10}ON_4$として

計算値　C 56.83；　H 5.30；
N 29.46

実験値　C 56.95；　H 5.38；
N 29.11

(ロ) 水素化アルミニウムリチウム0.7gをテトラヒドロフラン50mlに加え、氷冷下にこれに2,3－ジメチル－7－ホルミルアミノピラゾロ〔1,5－a〕ピリミジン1.0gをテトラヒドロフラン30mlに溶かした溶液を滴加する。70℃に5時間加熱撹拌し、水酸化ナトリウム溶液を加えて分解し、テトラヒドロフラン層をとり、濃縮後クロロホルムで抽出し、水酸化ナトリウム溶液で洗浄し、硫酸マグネシウムで乾燥する。溶媒を留去して残渣をエーテルより再結晶すれば、mp146℃の無色板状晶として2,3－ジメチル－7－メチルアミノピラゾロ〔1,5－a〕ピリミジン0.83gを得る。

元素分析　$C_9H_{12}N_4$として

計算値　C 61.34；　H 6.86
N 31.80

実験値　C 61.50；　H 7.01
N 31.80

例　2

(イ) 2,3,6－トリメチル－7－アミノピラゾロ〔1,5－a〕ピリミジン2.0gとギ酸酢酸混合酸無水物10mlを前例同様に反応させ、室温に1日放置後減圧濃縮し、残渣をアセトンより再結晶すれば、mp183℃（発泡）の淡緑色針状晶として2,3,6－トリメチル－7－ホルミルアミノピラゾロ〔1,5－a〕ピリミジン1.6gを得る。

元素分析　$C_{10}H_{12}ON_4$として

計算値　C 58.81；　H 5.92；
N 27.44

実験値　C 58.79；　H 6.10；
N 27.53

(ロ) 2,3,6－トリメチル－7－ホルミルアミノピラゾロ〔1,5－a〕ピリミジン250mgをテトラヒドロフラン中、水素化アルミニウムリチウム200mgを用いて前例同様に還元し、粗製物をアセトンより再結晶すれば、mp157℃の無色菱状晶として2,3,6－トリメチル－7－メチルアミノピラゾロ〔1,5－a〕ピリミジン205mgを得る。

元素分析　$C_{10}H_{14}N_4$として

計算値　C 63.13；　H 7.42；
N 29.25

実験値　C 63.24；　H 7.42
N 29.16

例　3

(イ) 2,5－ジメチル－3－フエニル－7－アミノピラゾロ〔1,5－a〕ピリミジン1.2gに氷水冷却下ギ酸酢酸混合酸無水物20mlを加える。冷却浴を去り、室温で8時間撹拌し、さらに室温に一夜放置後減圧濃縮する。結晶性残渣をエーテルで洗浄後アセトンより再結晶すれば、mp184℃（decomp.）の淡黄色立方晶として2,5－ジメチル－3－フエニル－7－ホルミノアミノピラゾロ〔1,5－a〕ピリミジン1.12gを得る。

$IR\ \nu_{max}^{Nujol}\ cm^{-1}$：3176，1700，1613

(ロ) 2,5－ジメチル－3－フエニル－7－ホルミルアミノピラゾロ〔1,5－a〕ピリミジン1.0gをテトラヒドロフラン中、水素化アルミニウムリチウム0.7gを用いて前例同様に還元し、粗製物をアセトンより再結晶すれば、mp190～191℃の無色プリズム晶として2,5－ジメチル－3－フエニル－7－メチルアミノピラゾロ〔1,5－a〕ピリミジン0.82gを得る。

$IR\ \nu_{max}^{Nujol}\ cm^{-1}$：3215，1629，1587，770

例　4

(イ) 2－ベンジル－3,5－ジメチル－7－アミノピラゾロ〔1,5－a〕ピリミジン0.75gに、氷水冷却下ギ酸酢酸混合酸無水物15mlを加える。冷却浴を去り、室温で5時間撹拌し、室温に一夜放置後減圧濃縮する。結晶性残渣をエーテルで洗

122℃の無色菱晶として2－ベンジル－3,5－ジメチル－7－ホルミルアミノピラゾロ〔1,5－a〕ピリミジン0.64gを得る。

IRν_{max}^{Nujol} cm^{-1} : 3200, 1691, 1624, 1178, 1167, 1129

(ロ) 2－ベンジル－3,5－ジメチル－7－ホルミルアミノピラゾロ〔1,5－a〕ピリミジン540mgをテトラヒドロフラン中、水素化アルミニウムリチウム400mgを用いて前例同様に還元すれば油状物として2－ベンジル－3,5－ジメチル－7－メチルアミノピラゾロ〔1,5－a〕ピリミジン320mgを得る。

IR$\nu_{max}^{CHCl_3}$ cm^{-1} : 3400, 1625, 1595, 1095

ピクラート：mp 207～208℃、黄色柱状晶。

特許請求の範囲

1 2,3,5,6位に置換基を有しまたは有しない7－アミノピラゾロ〔1,5－a〕ピリミジンをホルミル化剤と反応させて対応する7－ホルミルアミノ体とし、次いで水素化金属錯化合物で還元して7－メチルアミノ体を得ることを特徴とする新規7－メチルアミノピラゾロ〔1,5－a〕ピリミジン誘導体の製造法。